Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/IL05/000173

International filing date: 10 February 2005 (10.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/543,389
Filing date: 11 February 2004 (11.02.2004)

Date of receipt at the International Bureau: 14 April 2005 (14.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

PCT/IL2005/000173
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February 23, 2005

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APPLICATION NUMBER: ***60/543,389***
FILING DATE: ***February 11, 2004***

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

U.S. PTO 60/543389 022804 021104

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Additional inventors are being named on the second *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

SYNERGISTIC COMPOSITIONS FOR TREATMENT OF CANCER AND INFLAMMATION

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 17
☐ Drawing(s) *Number of Sheets*
☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

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Respectfully submitted,

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REGISTRATION NO. 52,993 *(if appropriate)*

Docket Number: 25992

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Docket Number 25992

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Number 2 of 2

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MAIL STOP PROVISIONAL PATENT APPLICATION
Attorney Docket: 25992

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Inventor (s): Nadir ARBER, Shahar LEV-ARI and Dov LICHTENBERG

Serial Number: NOT YET ASSIGNED

Filed: February 11, 2004

Title: **SYNERGISTIC COMPOSITIONS FOR TREATMENT OF CANCER AND INFLAMMATION**

TRANSMITTAL LETTER

Commissioner for Patents
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Submitted herewith for filing in the U.S. Patent and Trademark Office are the following **PROVISIONAL APPLICATION:**

1) Provisional Application Cover Sheet
2) 17 page Provisional Application consisting of:
   15 pages Textual Specification
   2 pages 11 claims;
3) Check No. 20587 $80.00 for filing fee as a small entity
4) Postcard for early notification of serial number

The Commissioner is hereby authorized to charge any deficiency or credit any excess to Deposit Account No. 14-0112

Respectfully submitted,
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SYNERGISTIC COMPOSITIONS FOR TREATMENT OF CANCER AND INFLAMMATION

FIELD OF THE INVENTION

This invention relates in general to the field of cancer and anti-inflammatory treatment.

BACKGROUND OF THE INVENTION

COX or prostaglandin H synthase is the enzyme that catalyzes rate-limiting steps in the biosynthesis of prostaglandins (PGs). In contrast to COX-1, the constitutive form that plays an important role in cell homeostasis, COX-2, also known as the "bad COX", is the inducible form and mainly involved in the onset of inflammation and mitogenic responses (Dubois et al., Cyclooxygenase in biology and disease, *FASEB J.* 12, 1063-1073 (1998) and Williams et al., The role of cyclooxygenase in inflammation, cancer, and development, *Oncogene*, 18, 7908-7916 (1999)). Since the identification and cloning of the COX-2 gene, accumulating evidence supports the critical role of COX-2 in carcinogenesis. Upregulation of COX-2 expression and PG production are commonly found in many cancer cells such as colorectal cancer and a number of COX-2 inhibitors such as non-steroidal anti-inflammatory drugs (NSAIDs) are able to block the COX enzymes and reduce PGs throughout the body. As a consequence, NSAIDs induce growth inhibition (a combination effects of inhibition of proliferation and induction of apoptotic cell death) in cancer cells. They also inhibit angiogenesis and can reduce ongoing inflammation, pain and fever.

Several mechanisms have been proposed to explain why COX-2 expression in neoplastic tissue enhances tumor growth. There is evidence suggesting that COX-2-produced PGE_2 causes amplification of tumor cell proliferation, inhibition of tumor cell apoptosis, enhancement of stromal cell angiogenesis and decreased immune surveillance of tumor cells.

PGs protect the gastrointestinal mucosa. They also play an important role in platelets and blood clotting function. Hence, NSAIDs can cause ulcers in the stomach and promote bleeding.

Celecoxib, also known as Celebrex, is the foremost branded non-steroidal and anti-inflammatory drug and the leading COX-2 specific inhibitor. Celecoxib has been shown to provide relief of the pain and inflammation of osteoarthritis, adult rheumatoid arthritis, acute pain, and primary dysmenorrheal in adults. In addition celecoxib has been shown to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis. Celecoxib has also been used in combinations with other substances. One such example is disclosed in US Patent No. 6,573,290 to Love in which a method for treating cancers comprising the administration of a combination of celecoxib and alpha-difluoromethylornithine (DFMO) to a patient in need thereof is disclosed.

Curcumin also shows similar COX-2 inhibition activity. US Patent Application No. 2003/0108628 discloses compositions comprising curcuminoid species such as curcumin along with diterpene lactones that in combination exhibit a synergistic effect on specific inhibition of inducible COX-2 activity and have minimal effect on COX-1 activity.

Unlike celecoxib which is thought to cause adverse effects that might militate against long-term administration, curcumin is a natural product of low toxicity. Curcumin inhibits COX-2 at the transcriptional level in cells in vitro. Although it displays low bioavailability, concentrations inhibitory to COX-2 are attainable in the colonic mucosa of rats after dietary administration. However, the doses needed to achieve such tissue concentrations far exceed those normally consumed as turmeric in the diet. Curcumin, known to inhibit various signaling pathways, is an important player in the induction of expression of the gene for COX-2 by inflammatory and tumor-promoting stimuli. It is thus likely to inhibit transcription of the gene at more than one level.

SUMMARY OF THE INVENTION

The present invention is based on the observations that a combination of curcumin and celecoxib showed a synergistic effect in reducing the number of colon adenocarinoma cancer cells, and a combination of curcumin and sulindac showed a synergistic effect in inhibiting the growth of colonic tumor cells. It is also suggested that this combination posses anti-inflammatory properties.

This synergistic effect paves the way to reduce the dose of each compounds, and in particular the high and toxic dose of celecoxib, allowing improving the safety profile of this regimen. A decrease in the toxicity as evident by a decrease in the undesirable side effects while maintaining the efficacy of the treatment.

Thus, by one aspect, the present invention provides a method for the synergistic inhibition of cancer cell growth, that is both more efficient and significantly safer then each drug alone. The method comprises contacting the cancer cells with a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of at least one NSAID drug, so that the effect in reduction of cancer cells is higher than the sum of effects on reduction of cancer cell growth when curcumin or the at least one NSAID drug are administered separately.

The present invention further concerns a method for treatment of cancer comprising administering to an individual in need of as an a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of at least one NSAID drug, so that the effect in the treatment of cancer is higher than the sum of effects on reduction of cancer growth cell when curcumin or the at least one said NSAID drug are administered separately.

By another aspect the present invention concerns a method for the reduction of inflammation comprising administering to a patient in need of as an

anti-inflammatory treatment a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of at least one NSAID drug, so that the effect in reduction of inflammation is higher than the sum of effects on reduction of inflammation when curcumin or the at least one said NSAID drug are administered separately.

By another aspect of the present invention, there is provided a method of reducing a dosage size of an at least one NSAID drug in the treatment of a patient in need of an NSAID drug therapy, comprising simultaneous administering of curcumin or an analogue or derivative thereof and said at least one NSAID drug, the curcumin being in an amount sufficient to reduce the NSAID drug concentration needed while maintaining the same therapeutic effect as compared to administering the NSAID drug alone.

In one specific case the method is used for the treatment of cancer. In another specific case, the method is used for the treatment of inflammation.

The concentration of the curcumin or an analogue or derivative thereof needed to achieve the therapeutic effect as compared to administering the at least one NSAID drug alone, may be measured by testing several varying combinations of curcumin and the at least one NSAID. Any combination containing curcumin and the at least one NSAID, for which the NSAID drug concentration is low, yet maintaining therapeutic efficacy, as compared to concentrations of NSAID alone, in *in vitro*, *in vivo* and clinical tests, would be considered as the combination obtained by the method above.

The NSAID drugs may be, without limiting the invention thereto, celecoxib, sulindac, sulindac sulfide, exisulind, ibuprofen, naproxen, rofecoxib, nimesulide, aspirin, piroxicam, oxaprozin, meloxicam, ketoprofen, etodolac, diflunisal and the like. Preferably the NSAID drug is celecoxib, sulindac, or sulindac sulfide.

In one preferred embodiment the NSAID drug is celecoxib. In another embodiment the NSAID drug is a drug other than celecoxib.

Accordingly, the present invention provides a method for the reduction of cancer cell growth comprising contacting the cancer cells with a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of celecoxib, so that the effect in reduction of cancer cells is higher than the sum of effects on reduction of cancer cell growth when curcumin or celecoxib are administered separately.

Additionally, the present invention provides a method for the reduction of cancer cell growth comprising contacting the cancer cells with a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of an NSAID drug being different from celecoxib, so that the effect in reduction of cancer cells is higher than the sum of effects on reduction of cancer cell growth when curcumin or said drug being different from celecoxib are administered separately.

The present invention further concerns a method for the treatment of cancer comprising administering to an individual in need of prevention or treatment of anti–cancer therapy a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of celecoxib, so that the effect in the treatment of cancer is higher than the sum of effects on reduction of cancer growth cell when curcumin or celecoxib are administered separately.

The present invention also concerns a method for the reduction of inflammation comprising administering to a patient in need of as an anti-inflammatory treatment a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of celecoxib, so that the effect in reduction of inflammation is higher than the sum of effects on reduction of inflammation when curcumin or celecoxib are administered separately.

By another preferred embodiment, the NSAID drug is sulindac.

Accordingly, the present invention provides a method for the reduction of cancer cell growth comprising contacting the cancer cells with a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of sulindac, so that the effect in reduction of cancer

cells is higher than the sum of effects on reduction of cancer cell growth when curcumin or sulindac are administered separately.

The present invention further concerns a method for the treatment of cancer comprising administering to an individual in need of as an anti–cancer therapy a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of sulindac, so that the effect in the treatment of cancer is higher than the sum of effects on reduction of cancer growth cell when curcumin or sulindac are administered separately.

The present invention also concerns a method for the reduction of inflammation comprising administering to a patient in need of as an anti-inflammatory treatment a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of sulindac, so that the effect in reduction of inflammation is higher than the sum of effects on reduction of inflammation when curcumin or sulindac are administered separately.

By another preferred embodiment, the NSAID drug is sulindac sulfide.

Accordingly, the present invention provides a method for the reduction of cancer cell growth comprising contacting the cancer cells with a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of sulindac sulfide, so that the effect in reduction of cancer cells is higher than the sum of effects on reduction of cancer cell growth when curcumin or sulindac sulfide are administered separately.

The present invention further concerns a method for the treatment of cancer comprising administering to an individual in need of as an anti–cancer therapy a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of sulindac sulfide, so that the effect in the treatment of cancer is higher than the sum of effects on reduction of cancer growth cell when curcumin or sulindac sulfide are administered separately.

The present invention also concerns a method for the reduction of inflammation comprising administering to a patient in need of as an anti-inflammatory treatment a synergistically effective amount of curcumin or an

analogue or derivative thereof and a synergistically effective amount of sulindac sulfide, so that the effect in reduction of inflammation is higher than the sum of effects on reduction of inflammation when curcumin or sulindac sulfide are administered separately.

The term "***inhibition of cancer cells growth***" as used in the present application refers to at least one of the following: decrease in the number of cells (due to cell death which may be necrotic, apoptotic or a combination thereof) as compared to control, decrease in tumor size, decrease in rate of tumor growth, inhibition of proliferation, stasis of tumor size, decrease in the number of metastasis, decrease in the number of additional metastasis, decrease in the invasiveness of the cancer, decrease in the rate of progression of the tumor from one stage to the next as well as decrease in the angiogenesis induced by the cancer.

The term "***treatment of cancer***" refers to at least one of the following: decrease in the rate of growth of the cancer (i.e. the cancer still grows but at a lower rate); cease of cancer growth, i.e. stasis of the cancer tumor occurs, and, in preferred cases, the cancer tumor diminishes or is reduced in size. The term also concerns reduction in the number of metastasis, reduction in the number of new metastasis formed, slowing of the progression of the cancer from one stage to the other and decrease in angiogenesis induced by the cancer. In most preferred cases, the cancer tumor is totally diminished. This term also concerns prevention for prophylactic situations or for those patients susceptible to contracting cancer, the administration of said compounds will reduce the likelihood of the individuals contracting the disease. In preferred situations, the individual to whom the compound is administered does not contract disease.

The term "***reduction of inflammation***", refers to at least one of the following: decrease in the number of infiltrating leukocytes, and in particular monocytes and lymphocytes to the site of injury; decrease in the amount of cytokines and mediators secreted by the infiltrating cells, decrease in at least one clinical manifestation of inflammation such as swelling, redness, pain, restriction of movement, fever, warmth, etc.

The term "***synergistically effective amount***" in the context of the present invention, refers to an amount which is both therapeutically active (with the other component) and shows synergistic effect as will be explained bellow. A therapeutically effective amount is determined by such considerations as may be known in the art. The amount must be effective to achieve the desired therapeutic effect as described above (i.e. treatment of cancer, reduction in cancer cell growth, reduction in inflammation), *inter alia*, on the type and severity of the disease to be treated and the treatment regime. The effective amount is typically determined in appropriately designed clinical trials (dose range studies) and the person versed in the art will know how to properly conduct such trials in order to determine the effective amount. As generally known, an effective amount depends on a variety of factors including the distribution profile within the body, a variety of pharmacological parameters such as half life in the body, on undesired side effects, if any, on factors such as age and gender, etc. The term "***synergistically effective amount***" in this context refers to an amount wherein the combined effect of two different components administered together creates a greater effect than the sum of the actions produced by each acting independently. The effect is in relation to the described under the terms "reduction of growth of cancer cells", "treatment of cancer" or "reduction of inflammation".

The term "***cancer***" in accordance with the present invention refers to solid tumors as well as to tumors of the neuronal system and tumors of the haematopoetic system. Solid tumors such as adenocarcinomas, sarcomas, testicular and ovarian dysgerminoma, retinoblastoma, Wilm's tumor, neuroblastoma, malignant malinoma and mesothelioma. Preferably, the compositions may be used for treating adenocarcinoma tumors selected from small cell lung cancer, kidney cancer, uterus cancer, prostate cancer, bladder cancer, ovary cancer, and colorectal cancer and most preferably colon adenocarcinoma.

The term "***inflammation***" refers in the context of the present invention to any disease wherein a response to insult which followed by invasion of leukocytes

(notably monocytes and lymphocytes) to the insult site, followed by massive secretion of cytokines and various other cell mediators.

Examples of inflammation related diseases or disorders are arthritis, including rheumatoid arthritis, spondyloathopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. The compositions may also be used to treat asthma, bronchitis, menstrual cramps, tendonitis, bursitis, psoriasis, dermatitis, Crohn's disease, gastritis, irritable bowel syndrome, and ulcerative colitis.

The synergistic amount of curcumin or an analogue or derivative thereof used in the method of the invention, refers to concentrations of 70%, 60%, 50%, 40%, 30%, 20%, 10% or 5% w/w as compared to the total weight of the active ingredient administered without the carrier (i.e. when "70%" is mentioned it refers to 70% of celecoxib and 30% of curcumin as well as to 70% of curcumin and 30% of celecoxib). Mid-way concentrations such as 63% or 34.2 % or smaller or higher concentrations are also encompassed within the scope of the invention. Additionally, it should be clear that the ratio of curcumin to the second component of the present invention may be presented by way of molar ratio or weight ratio or by any other known unit rather then percent w/w ratio.

The compounds may be administered with pharmaceutically acceptable carriers, excipients and/or other additives.

The term "***administration***" or "***administering***" as used herein is meant any way of administration such as parenteral, oral, and rectal, sun-lingual and the like. By "***parenteral***" is meant intravenous, subcutaneous and intramuscular administration. The method of administration shall vary according to, inter alia, the particular formulation, the dosage, etc.

Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention are given by way of illustration only, since various modifications within the spirit and scope of the invention will become apparent to

those skilled in the art from this detailed description. Such modifications are also intended to be within the scope of the invention.

Materials and methods

1. Reagents and chemicals

Celecoxib was provided by Pfizer (New York, NY, USA). Sulindac and Sulindac Sulfide were provided by Cell Pathways Inc. (Horsham, PA, USA). All other reagents with the highest purity were purchased from Sigma Chemical Co. (St. Louis, MO, USA).

2. Cancer cell culture

The growth inhibition of celecoxib, sulindac, sulindac, sulindac sulfide, curcumin or an analogue or derivative thereof such as demethoxycurcumin and bisdemethoxycurcumin, and combination of curcumin with celecoxib, with sulindac or with sulindac sulfide was tested on the following cell lines:

1. Human colon adenocarcinoma cell line HT-29 obtained from the American Type Culture Collection (ATCC) and

2. Human colon adenocarcinoma cell line SW-480 obtained from the American Type Culture Collection (ATCC) and

3. Human colon adenocarcinoma cell line Caco-2 obtained from the American Type Culture Collection (ATCC) and

4. Normal enterocytes derived from the rat Ileum transformed by c-K-Ras (Arber, N., Sutter, T., Miyake, M., Kahn, S., Venkatraj, V. S., Sobrino, A., Warburton, D., Holt, P. R., Weinstein, I. B. Increased expression of cyclin D1 and the Rb tumor suppressor gene in c-K-ras transformed rat enterocytes. Oncogene, 12:1903-1908, 1996).

The different cell lines were grown and maintained in DMEM (Haemek, Israel) supplemented with 5% fetal calf serum (FCS), penicillin and streptomycin at 37^0C, in an atmosphere of 95% oxygen and 5% CO2. G418 was used as the selectable marker in IEC18- *ras* transformed cells

3. Assays for Growth Inhibition of cancer cells

Cells were plated in duplicate at a density of $3X10^4$ in 12 wells plates, containing 1 mL of Dulbecco's modified Eagle's medium (DMEM, Beit-Haemek, Israel) supplemented with 5% fetal calf serum (FCS), 1% penicillin and 1% streptomycin at 37^0C, in an atmosphere of 95% oxygen and 5% CO_2. Celecoxib, curcumin or 0.1% dimethyl sulfoxide (the drug vehicle), were added to the culture medium 24 hours after plating at the selected concentrations as shown in **Tables 1-5**. The numbers of viable cells after incubation with these compounds for 72 hours was determined in duplicates using a Coulter counter. All experiments were repeated at least three times and gave similar results. The different combinations of celecoxib and curcumin were used similarly and the viable cells were similarly counted.

The same procedure was repeated for curcumin and sulindac and for curcumin and sulindac sulfide.

As may be appreciated from **Table 1**, compositions 9, 10 and 11 showed synergistic effects. The efficacy of the compositions of the present application may be further illustrated by comparing the data presented for compositions 8 and 9. Composition 9 comprising a combination of 5μM of celecoxib and curcumin showed a very similar efficacy as compared to composition 8 which comprised 50μM celecoxib with no curcumin. This order of magnitude lowered dosage of celecoxib is clinically important as it can be achieved in the serum of patients receiving standard anti-inflammatory dose of celecoxib. It may be associated with even lower profile of toxic side effects of chronic treatment with the drug.

Composition No.	Sample (in μM)	Viable Cells (%)	% Synergism
1	control-72h	100.00	----
2	Curcumin 5	94.78	----
3	Curcumin 10	69.78	----

4	Curcumin 15	42.14	----
5	Celecoxib 5	79.27	----
6	Celecoxib 10	68.58	----
7	Celecoxib 15	50.88	----
8	Celecoxib 50	14.20	----
9	Celecoxib 5+ Curcumin 10	12.28	75.0%
10	Celecoxib 5 + Curcumin 15	8.21	70.4%
11	Celecoxib 10 + Curcumin 10	22.18	42.2%
12	Celecoxib 10+ Curcumin 15	15.99	No effect
13	Celecoxib 15 + Curcumin 10	24.45	No effect
14	Celecoxib 15 + Curcumin 15	16.39	No effect

Table 1: Effect of curcumin, celecoxib, curcumin+celecoxib on HT-29 cells' growth.

Treating the cells with curcumin and sulindac, as shown in **Table 2** at a concentration of 400μM sulindac and 10 μM curcumin showed synergism of about 15%. It may be further noted, that the combinations utilizing 400μM sulindac, exhibited better efficacy as compared with the 400 or 600μM compositions which contained no curcumin.

Composition No.	**Sample (in μM)**	**Viable Cells (%)**	**% Synergism**
15	control-72h	100.00	----
16	Curcumin 10	69.3	----
17	Curcumin 15	40.0	----
18	Sulindac 400	63.6	----
19	Sulindac 600	37.1	----
20	Sulindac 400 + curcumin 10	27.9	15.2%
21	Sulindac 400 + curcumin 15	10.9	No effect
22	Sulindac 600 +	12.2	No effect

	curcumin 10		
23	Sulindac 600 + Curcumin 15	6.7	No effect

Table 2: Effects of sulindac, curcumin and a combination thereof on HT-29 cells' growth.

Treating the cells with curcumin and sulindac sulfide, as shown in **Table 3** at a concentration of 30μM sulindac sulfide and 10 μM curcumin showed synergism of about 30%. In addition a concentration of 60μM sulindac sulfide and 10 μM curcumin showed synergism of about 9%. Moreover it may be noted, that the other combinations of sulindac sulfide, exhibited better efficacy as compared with the 30 or 60μM compositions which contained no curcumin.

composition No.	Sample (in mM)	Viable Cells (%)	% Synergism
24	control-72h	100.0	----
25	curcumin 10	71.3	----
26	curcumin 15	40.2	----
27	sulindac sulfide 30	78.9	----
28	sulindac sulfide 60	34.0	----
29	sulindac sulfide 30 + curcumin 10	20.4	29.8
30	sulindac sulfide 60 + curcumin 10	19.9	No effect
31	sulindac sulfide 30 + curcumin 15	10.2	8.92
32	sulindac sulfide 60 + curcumin 15	11.1	No effect

Table 3: Effects of sulindac sulfide, curcumin and a combination thereof on HT-29 cells' growth.

4. Assays for inflammation inhibition of inflammation cells

Culture of human RA synovial fibroblasts (RASFs)

RASFs were prepared from synovial tissue as described in the literature (Kawai S, Nishida S, Kato M, Furumaya Y, Okamoto R, Koshino T, et al. Comparison of cyclooxygenase-1 and -2 inhibitory activities of various nonsteroidal anti-inflammatory drugs using human platelets and synovial cells. Eur J Pharmacol 1998; 347:87–94). The synovial tissue specimens were obtained during total knee replacement surgery in patients with RA. Synovial tissue is digested for 2 hours with 0.2% (weight/volume) bacterial collagenase and then suspended in DMEM with 10% (volume/volume) FCS, 100 units/ml penicillin, and 100 g/ml streptomycin. The cells were incubated at 37°C in 5% CO2 for several days, after which nonadherent cells are removed. Fibroblast-like adherent cells from the first or second passage were used as RASFs.

Cell viability

RASFs (1.5 X10^4/well) were incubated at 37°C in 96-well plastic plates with test drugs in DMEM containing 10% FCS in an atmosphere of 5% CO_2 (final DMSO concentration 0.1%). After 48-72 hours, cell viability was assessed by ability of metabolically active cells to reduce tetrazolium salt (XTT) to coloured formazan compounds. The absorbance of the samples was measured with an ELISA reader (wavelength 450 nm; reference wavelength 630 nm). Each measurement was done in triplicate.

As may be appreciated from **Table 4**, all compositions showed synergistic effects. Composition 40 showed the most remarkable synergistic effect of 65.4%. The potentiation of celecoxib effect by curcumin is important as it may enable to reduce celecoxib doses. This may be associated with even lower profile of toxic side effects of chronic treatment with the drug.

composition No.	Sample (in mM)	Viable Cells (%)	% Synergism
33	control-72h	100.0	----
34	celecoxib 20	115.9	----
35	celecoxib 40	106.5	----
36	curcumin 30	105.4	----
37	curcumin 40	37.7	----
38	celecoxib 20 + curcumin 30	73.5	26.5
39	celecoxib 20 + curcumin 40	27.6	10.0
40	celecoxib 40 + curcumin 30	34.6	65.4
41	celecoxib 40 + curcumin 40	27.6	10.1

Table 4: Effects of celecoxib, curcumin and a combination thereof on RASF cells' viability.

CLAIMS:

1. A method for the reduction or inhibition of cancer cell growth comprising contacting the cancer cells with a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of at least one NSAID drug, so that the effect in reduction of cancer cells is higher than the sum of effects on reduction of cancer cell growth when curcumin or the at least one NSAID drug are administered separately.

2. A method for the treatment of cancer comprising administering to an individual in need of as an anti–cancer therapy a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of at least one NSAID drug, so that the effect in the treatment of cancer is higher than the sum of effects on reduction of cancer growth cell when curcumin or the at least one said NSAID drug are administered separately.

3. A method for the reduction of inflammation comprising administering to a patient in need of as an anti-inflammatory treatment a synergistically effective amount of curcumin or an analogue or derivative thereof and a synergistically effective amount of at least one NSAID drug, so that the effect in reduction of inflammation is higher than the sum of effects on reduction of inflammation when curcumin or the at least one said NSAID drug are administered separately.

4. A method of reducing a dosage size of an at least one NSAID drug in the treatment of a patient in need of an NSAID drug therapy, comprising simultaneous administering of curcumin or an analogue or derivative thereof and said at least one NSAID drug, the curcumin being in an amount sufficient to reduce the at least one NSAID drug concentration

needed while maintaining the same therapeutic effect as compared to administering the NSAID drug alone.

5. A method according to claim 4 for the treatment of cancer.

6. A method according to claim 4 for the treatment of inflammation.

7. A method according to any one of claims 1 to 6, wherein said NSAID drug is selected from celecoxib, sulindac, sulindac sulfide, exisulind, ibuprofen, naproxen, rofecoxib, nemisulide, aspirin, piroxicam, oxaprozin, meloxicam, ketoprofen, etodolac, and diflunisal.

8. A method according to claim 7 wherein said NSAID drug is celecoxib.

9. A method according to claim 7 wherein said NSAID drug is sulindac.

10. A method according to claim 7 wherein said NSAID drug is sulindac sulfide.

11. A method according to any one of the preceding claims wherein the curcumin analogue or derivative is selected from the group consisting of demethoxycurcumin and bisdemethoxycurcumin.